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6/22/87

DATA EVALUATION REPORT

STUDY TYPE: Chronic/Oncogenicity study in mice

TOX. CHEM. NO.: 868B

ACCESSION NUMBER: ?

MRID NO.: 401611-06

TEST MATERIAL: tefluthrin 12892

SYNONYMS: PP993

STUDY NUMBER(S): CTL/P/1509

SPONSOR: ICI Americas

TESTING FACILITY: ICI Toxicology Laboratory, Arderley, UK

TITLE OF REPORT: Tefluthrin: Lifetime feeding study in mice

AUTHOR(S): G.A. Wickramaratne

REPORT ISSUED: Dec. 18, 1986

CONCLUSIONS: 50/sex/group were fed diets containing 0, 25 (22.6ppm or 3.4 mg/kg), 100 (90.2ppm or 13.5mg/kg) or 400 (363ppm or 54.4 mg/kg) ppm tefluthrin for 104 weeks. There was a slight reduction in body weight gain in the high dose males and females, amounting to about 6%, with an accompanying reduction in food consumption for the first two weeks of treatment. Food efficiency in high dose males was also decreased for the first 4 weeks, but increased to control levels after 4 weeks. There was a slight decrease in white cell and lymphocyte counts at week 78 in high dose males, but no effects were apparent at 104 weeks. No gross pathology tables were submitted for this study. There were several non-neoplastic changes seen in the mid and high dose, including hemangiomatous changes seen in the uterus of mid and high dose females, and liver necrosis seen in mid and high dose females and telangiectasis seen in high dose females. Neoplastic changes seen with significant positive trends included liver type A nodules seen in the mid and high dose females, Harderian gland adenomas seen in high dose males, pituitary gland adenomas seen in high dose males and adenomas and carcinomas of the pars intermedia seen in high dose females. It does not appear that an MTD has been reached in this study.
NOEL = 3.4 mg/kg, LEL = 13.5 mg/kg based on hemangiomatous changes seen in uterus and liver necrosis
Oncogenic NOEL = 3.4 mg/kg based on an increase in pituitary adinomas and type "A" liver nodules seen at 13.5 mg/kg

Classification: core-Supplementary: Gross pathology tables are missing and no comments on gross pathology were evident in the study text. There are two sets of appendicies numbered with similar numbers. An explanation will need to be given by the Firm concerning how

the organ weights were "adjusted" with to the body weights. Historical controls will need to be submitted on "type A" and "B" liver nodules, Harderian gland adenomas, lung adenocarcinomas, and pituitary gland adenomas and carcinomas and adenomas and carcinomas of the pars intermedia

A. MATERIALS:

1. Test compound: Tefluthrin,
Description: pale, yellow waxy solid
Batch # P16, Y01059/002
Purity 95.1%, contaminants: list in CBI appendix

2. Test animals: Species: SPF mice, Strain:Alpk:AP, Age: 21 days
Weight: not given, Source: Animal Breeding unit, old when supplied
ICI Alderley Park, UK
Animals were transported in such a way as to insure SPF status.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (ppm)	Main Study months male	female
1 Cont.	0	50	50
2 Cont.	0	50	50
3 Low (LDT)	25 (22.5)	50	50
4 Mid (MDT)	100 (90.2)	50	50
5 High(HDT)	400 (363)	50	50

2. Diet preparation

Diet was prepared in 30 or 60 kg batches and stored at an unspecified temperature. The study text states that details for the diet preparation and despensing could be found in in appendix 3, However, there are two appendices 3.
Concentration: Samples were taken from the first batch and at 4 week intervals at all dose levels for test dose content.
Stability: Tested over a 6-week period in a concurrent study.
Homogeneity- tested in a previous study.

Results: Two sets of appendices with similar numbers make finding these data very confusing. The stability data indicate that the compound is relatively stable in animal diet. The concentrations of of tefluthrin in the diet were stated to be within 10% of target concentrations, although a large proportion of diets gave values below nominal levels. Appended page 3 gives a breakdown of % deviations from nominal values. A summary of dietary analysis results is given on appended page 5.

below nominal levels. Appended page 3 gives a breakdown of % deviations from nominal values. A summary of dietary analysis results is given on appended page 5.

3. Animals received food (Ground CT1 diet, Special Diet Services Witham Essex England) and water ad libitum.

4. Statistics - The procedures utilized are on appended pages 1 and 2.

5. Quality assurance statement was signed and dated 12/16/86.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected once daily for signs of toxicity and mortality. More detailed clinical exams were performed weekly.

Mortality (survival): No treatment-related changes in survival were evident, see appended pages 5 and 6.
Toxicity: No treatment-related clinical signs were evident.

2. Body weight

Animals were weighed weekly for the first 12 weeks, then every 4th week thereafter.

Results: High dose males and females had a consistent reduction in body weight gain with approximately a 6% reduction in gowy weight gain. Males given 100 ppm tefluthrin showed a small reduction in body weight gain, seen mostly in the first few weeks of study but they recovered thereafter. At termination, the reduction was only 3% below controls. See appended pages 7 and 8 for details.

3. Food consumption and compound intake

Consumption was determined and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.

Results: Food consumption for the 400 ppm males and females was slightly reduced in the first 2 weeks, but climbed to control levels thereafter. See appended page 9.
Food Efficiency was decreased slightly in males in weeks 1-4 but was within control values thereafter.
Dose rates were calculated and were supposed to appear in appendix 11 but no appendix 11 exists.

4. Ophthalmological examinations were not performed.

5. Blood was collected by tail vein except at termination when the animals were bled by cardiac puncture, at 12 and 18 months for hematology from 10/sex/group. 10/sex were used at termination. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet count*		Reticulocyte count
	Blood Clotting Measurements	X	Bone marrow smears [a]
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies
[a] Were taken but not examined.

Results: White cell and lymphocyte count were slightly decreased at week 78 in males treated with 400 ppm tefluthrin, but this effect did not persist into week 104, and was not considered a treatment-related effect.

b. Clinical chemistries were not performed.

6. Urinalysis was not performed.

7. Sacrifice and Pathology -
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed. Paired organs were weighed together.

X	Digestive system	X	Cardiovasc./Hemat.	X	Neurologic
X	Mouth	X	.Aorta*	XX	.Brain*†
X	.Salivary glands*	X	.Heart*	X	Periph. nerve*#
X	.Esophagus*		.Bone marrow*	X	Spinal cord (3 levels)*#
X	.Stomach*	X	.Lymph nodes* [b]	X	.Pituitary*
X	.Duodenum*	X	.Spleen*	X	Eyes (optic n.)*#
X	.Jejunum*	X	.Thymus*		Glandular
X	.Ileum*		Urogenital	X	.Adrenals*
X	.Cecum*	XX	.Kidneys*†		Lacrimal gland#
X	.Colon*		.Urinary bladder*	X	Mammary gland*#
X	.Rectum*	XX	.Testes*†		.Parathyroids*††
XX	.Liver*† [a]	X	Epididymides	X	.Thyroids*††
	Gall bladder*#	X	Prostate	X	Harderian gland
X	.Pancreas*	X	Seminal vesicle	X	Bone*#
	Respiratory	X	Ovaries*†	X	Skeletal muscle*#
X	.Trachea*	X	.Uterus*	X	Skin*#
X	.Lung*	X	Cervix	X	All gross lesions
	Nose°	X	Preputial gland		and masses*
	Pharynx°				
X	Larynx°				
X	Nasal cavity [c]				

* Required for subchronic and chronic studies
° Required for chronic inhalation
In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies
[a] weighed with gall bladder, and microscopically examined together
[b] cervical and mesenteric
[c] perfused, submitted and stored

Microbiological sentinels (10/sex as controls or 400 ppm tefluthrin) were used to maintain the microbiological status of the animals, but the results of these animals are not pertinent to the conduct or conclusions of this study and will not be discussed further.

a. Organ weight: Liver weights in males both absolute and "adjusted" were elevated in all treatment groups. However, when type A or B nodules and histiocytic sarcoma were excluded, no changes from control weights were seen. No other treatment-related changes were evident. An explanation needs to be given concerning how the study authors "adjusted" the organ weights with the body weights.

b. Gross pathology: No summary tables were given for gross macroscopic changes. No mention was even made in the study text of gross changes, although macropathology data were noted on individual pathology sheets.

c. Microscopic pathology

1) Non-neoplastic: There appears to be a dose-related increase in hemangiomatous change in the uterus at the mid and high dose. See table I for details. In the liver there is an increase in females of hepatic necrosis at the mid and high dose, and an increase in telangiectasis in females at the high dose.

TABLE I
NON-NEOPLASTIC CHANGES

Tissue	Sex	0	25	100	400	Trend P value
Uterus						
Hemangiomatous change	F	3/99	0/49	3/50	6/48	p = 0.002
Liver						
Hepatic necrosis	F	2/100	2/49	4/50	5/50	p = 0.02
Telangiectasis	F	0/100	1/49	0/50	3/50	p = 0.004

2) Neoplastic: There appears to be increases in neoplastic changes in several organs with some very significant positive trends seen. These organs include the liver, with an increase in "type A" nodules. These nodules have been defined by the study sponsor as including hyperplastic nodules as well as benign tumors. Type "B" nodules are synonymous with hepatocellular carcinomas. When these are combined, there does not appear to be significance. Harderian gland adenomas appear to be increased at the high dose in males. Lung adenomas appear increased in high dose males. When they are combined with carcinomas there doesn't appear to be significance. Pituitary gland adenomas in males appear increased at the mid and high dose, and when combined with carcinomas, there still appears to be some increase in tumor rate. and adenomas of the pars intermedia are increased in high dose females. See table II for details.

TABLE II
NEOPLASTIC CHANGES

Tissue	Sex	0	0	25	100	400	Trend P value
Liver							
"type A nodule"	F	1/50	1/50	0/49	3/50	5/50	p = 0.004
"type B nodule"	F	2/50	0/50	3/49	1/50	1/50	
Harderian gland							
Adenoma	M	4/49	1/46	4/48	4/48	7/49	p = 0.04
Lung							
Adenoma	M	4/50	4/50	3/50	2/49	4/50	
Adenocarcinoma	M	0/50	2/50	0/50	1/49	3/50	p = 0.03
Pituitary gland							
Adenoma	M	1/45	1/43	0/34	2/34	4/41	p = 0.01
Carcinomas	M	0/45	0/43	0/34	1/34	0/41	
Adenoma of the pars intermedia	F	0/41	0/45	0/44	0/44	3/43	p = 0.003
Carcinoma of the pars intermedia	F	0/41	0/45	0/44	0/44	1/43	

DISCUSSION:
There was a slight reduction in body weight gain in the high dose males and females, amounting to about 6%, with an accompanying reduction in food consumption for the first two weeks of treatment. Food efficiency in high dose males was also decreased for the first 4 weeks, but increased to control levels after 4 weeks. There was a slight decrease in white cell and lymphocyte count at week 78 in high dose males, but no effects were apparent at 104 weeks. No gross pathology tables were submitted for this study. There were several non-neoplastic changes seen in the mid and high dose, including hemangiomatous changes seen in the uterus of mid and high dose females, and liver necrosis seen in mid and high females and telangiectasis seen in high dose females. Neoplastic changes with significant positive trends included liver type A nodules seen in mid and high dose females, Harderian gland adenomas seen in the high dose males, and pituitary gland adenomas and carcinomas seen in high dose males and adenomas and carcinomas of the pars intermedia seen in high dose females. Historical controls for these above neoplastic changes seen will have to be requested from the sponsoring firm.

NOEL = 3.4 mg/kg based on hemangiomatous changes seen in the uterus liver necrosis
LEL = 13.5 mg/kg

Oncogenic NOEL = 3.4 mg/kg based on an increase in an increase in pituitary adenomas and type "A" liver nodules seen at 13.5 mg/kg

Pages 8-17 Access to FIFRA Registration Data is restricted under FIFRA section 10(g)

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Chemical:	**Tefluthrin**
PC Code:	**128912**
HED File Code	**13000 Tox Reviews**
Memo Date:	**06/26/87 12:00:00 AM**
File ID:	**00000000**
Accession Number:	**412-04-0140**

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